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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/043,440	01/10/2002	Costas D. Maranas	P05468US1	1336

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EXAMINER

MORAN, MARJORIE A

ART UNIT	PAPER NUMBER
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1631

DATE MAILED: 08/18/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/043,440

Applicant(s)

MARANAS ET AL.

Examiner

Marjorie A. Moran

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 07 June 2005.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-8, 10-16, 19-27 and 30-32 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☒ Claim(s) 23, 25-27 and 29 is/are allowed.
- 6) ☒ Claim(s) 1-8, 10-16, 18-21, 24, and 30-32 is/are rejected.
- 7) ☒ Claim(s) 22 is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 6/7/05 has been entered.

Claims 1-8, 10-16, 19-27 and 30-32 are pending. Applicant's arguments and the SCHILLING declaration filed 3/17/05 have been fully considered but are moot in view of the new ground(s) of rejection set forth below.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 2, 21, 24 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 2 and 21 limit logic constraints to "include constraints selected to protect against..." It is unclear whether the logic constraints of claims 2 and 21 are intended to replace the logic constraints of parent claims 1 and 20, respectively, are intended to be in addition to the constraints of the parent claims (as would be indicated by the phrase – further include--), or are intended in some way to further limit the constraints of the

parent claims (as would be indicated by a phrase such as --wherein the logic constraints are those which...--). As the limitation intended in claims 2 and 21 is unclear, the claims are indefinite.

Claim 24 limits constraints to "include logic constraints selected to protect against..." It is unclear whether the logic constraints of claim 24 are intended to replace the regulatory and DNA microarray experimental data constraints of claim 23, are intended to be in addition to the constraints of claim 23 (as would be indicated by the phrase --further include--), or are intended in some way to further limit the constraints of claim 23. As the limitation intended in claim 24 is unclear, the claim is indefinite.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-8, 10-12, 14-15, 19-21, and 30-31 are rejected under 35 U.S.C. 102(b) as being anticipated by HATZIMANIKATIS et al. (AIChE Journal (May 1006) Vol. 42, no. 5, pp. 1277-1292).

HATZIMANIKATIS teaches a method and system for modeling cellular metabolic reactions by constructing a flux balance analysis model and applying a variety of constraints, including logical constraints and kinetic (reaction rate) constraints (p. 1282-

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1283), thus anticipating claims 1 and 19. HATZIMANIKATIS teaches that his constraints may also include regulatory constraints (p. 1283), thus anticipating claim 20. HATZIMANIKATIS teaches that his constraints may be represented by binary variables wherein presence of a regulatory loop (i.e. reaction) is represented by one and the absence is represented by zero (p. 1282-1282), thus anticipating claims 10-11. HATZIMANIKATIS teaches optimization and solving for desired metabolic outcomes using mixed-integer linear programming in his method and model (pp. 1282-1286), thus anticipating claims 4-6, 14-15, and 30-31. HATZIMANIKATIS teaches that solutions in his model are constrained to be those consistent with other requisite coupled metabolic reactions, thus inherently teaching connectivity constraints, and thereby anticipating claim 3. HATZIMANIKATIS teaches that his reaction rate expressions are constrained to be within physiological bounds, wherein zero value for fluxes are not physiologically acceptable, and teaches that one logical constraint is that one that forbids activation and inhibition of an enzyme by the same metabolite (p. 1282), thus teaching constraints that protect against violation of a kinetic or regulatory barrier, and anticipating claims 2, 7, and 21. HATZIMANIKATIS teaches that his logical constraints are those defined by a relationship between regulatory loops and changes in adjustable variables; i.e. fluxes (pp. 1282-1283), thereby anticipating claim 8. One of HATZIMANIKATIS' examples includes calculation of a minimal set of reactions for optimizing performance (p. 1286), thus anticipating claim 12.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 13, 16, and 32 are rejected under 35 U.S.C. 103(a) as being unpatentable over HATZIMANIKATIS et al. (AIChE Journal (May 1006) Vol. 42, no. 5, pp. 1277-1292) as applied to claims 1-8, 10-12, 14-15, 19-21, and 30-31, above.

HATZIMANIKATIS teaches a method and system for modeling cellular metabolic reactions, as set forth above. HATZIMANIKATIS teaches that the objective of his method is to optimize certain functions such as production of metabolites or growth (p. 1279). HATZIMANIKATIS further teaches that enzymes in organisms may be engineered or designed to produce a particular result based on the results of his model (pp. 1286 and 1288). HATZIMANIKATIS does not specifically teach identifying a

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minimal set of reactions capable of supporting a growth rate nor engineering a change in an organism based on a desired metabolic outcome.

It would have been obvious to one of ordinary skill in the art at the time of invention to have engineered cells, as suggested by the engineering of HATZIMANIKATIS, comprising the enzymatic changes taught by HATZIMANIKATIS where the motivation would have been to overexpress certain reactions in order to maximize production of a desired metabolite, as taught by HATZIMANIKATIS (pp. 1287 and 1288). It would further have been obvious to have calculated a minimal set of reactions capable of supporting growth using HATZIMANIKATIS' model, as suggested by HATZIMANIKATIS, where the motivation would have been to optimize any desired output of metabolic function of a cell, as taught by HATZIMANIKATIS (p. 1279).

Allowable Subject Matter

Claim 22 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. Claims 23, 25-27 and 29 are allowed.

The following is a statement of reasons for the indication of allowable subject matter: None of the prior art teaches or fairly suggests applying DNA experimental data constraints in a flux balance analysis model.

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Conclusion

Claims 23, 25-27 and 29 are allowed; claim 22 is objected to. Claims 1-8, 10-16, 18-21, 24, and 30-32 are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Marjorie A. Moran whose telephone number is (571) 272-0720. The examiner can normally be reached on Mon,Wed: 7-1:30; Tue,Thur: 7:30-6; Fri 7-3:30 EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on (571)272-0718. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Marjorie A. Moran
Primary Examiner
Art Unit 1631

Marjorie A. Moran
8/16/05